Pharmacokinetics
Unit III Part 2

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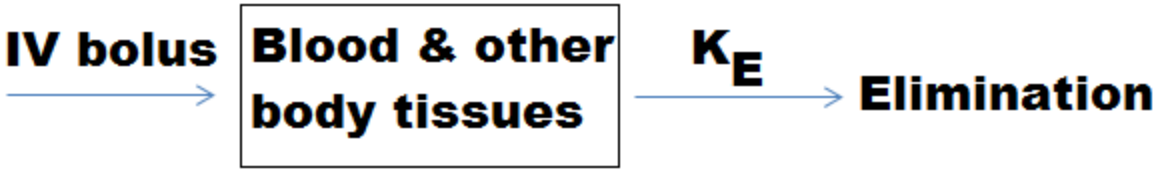
One compartment open model. (a). Intravenous Injection (Bolus) (b). Intravenous infusion and (c) Extra vascular administrations. Pharmacokinetics parameters - KE ,t1/2,Vd,AUC,Ka, Clt and CLR- definitions methods of eliminations, understanding of their significance and application

One compartment open model: Intravenous bolus administration



$\frac{dx}{dt} = Rate\ in$ (availability) $- Rate\ out\ (elimination)$

Because rate in or absorption is absent.

Therefore $\frac{dx}{dt} = -Rate\ out$

If rate out or elimination follows first order kinetics then

$\frac{dx}{dt} = -K_E X$

K_E = first order elimination rate constant

X= amount of drug in the body at any time t remaining to be eliminated.

−ve sign indicates loss of drug from the body.

$$\frac{dx}{x} = -K_E.dt$$

$$\int_{x}^{x_0} \frac{dx}{x} = -K_E \int_{0}^{t} dt$$

$$I_n\, x - I_n\, x_0 = -K_E.\, \mathrm{t}$$

$$I_n\, x = I_n\, x_0 - K_E.\, \mathrm{T}$$

$$X = X_o\, -e^{-K_E.\, t}$$

Above equation shows disposition of a drug that follows one compartment kinetics is monoexponential.

Estimation of Pharmacokinetic Parameters

- For a drug that follows one-compartment kinetics and administered as rapid i. v. injection, the decline in plasma drug concentration is only due to elimination of drug from the body (and not due to distribution), the phase being called as elimination phase.
- Elimination phase can be characterized by 3 parameters—
- 1. Elimination rate constant
- 2. Elimination half-life
- 3. Clearance

Elimination rate constant

$$K_E = K_e + K_m$$

K_e = rate constant for renal excretion

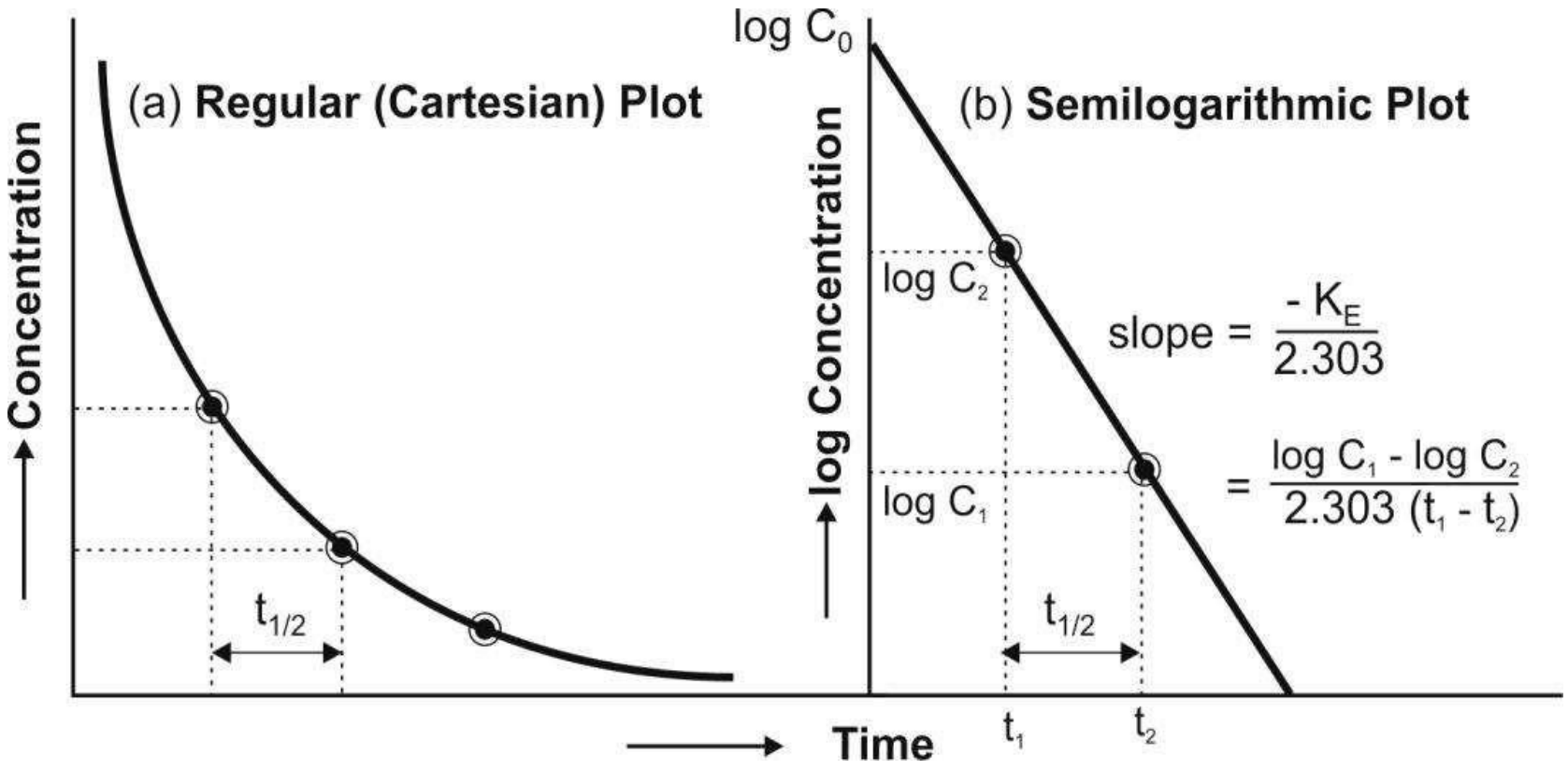
K_m = rate constant for metabolism

If K_e & K_m are known fraction of drug excreted unchanged in urine F_e and fraction of drug metabolised F_m can be given as

$$F_e = \frac{K_e}{K_E}$$

$$F_m = \frac{K_m}{K_E}$$

(a) Cartesian plot of a drug that follows one-compartment kinetics and given by rapid i.v. injection, and (b) Semi logarithmic plot for the rate of elimination in a one-compartment model.



Elimination half-life is defined as time taken for amount of the drug in the body as well as plasma concentration to decline by one-half or 50% its initial value.

$$t_{1/2} = \frac{0.693}{K_E}$$

Elimination half-life can also be expressed as

$$t1/2 = \frac{0.693Vd}{ClT}$$

Elimination half-life is secondary parameter that depends upon primary parameters clearance and apparent volume of distribution.

- *These parameters are closely related with the physiologic mechanisms in the body, they are called as* ***primary parameters.***
- 1. Apparent volume of distribution, and
- 2. Clearance.

Apparent Volume of Distribution

Apparant volume of distribution (V_d) is the hypothetical volume of body fluid in which the drug is dissolved. This is not true anatomic or physical volume.

$$V_d \times C_p = X$$

$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{X}{C}$$

Clearance

Clearance is defined as the theoretical volume of body fluid containing drug (i.e. that fraction of apparent volume of distribution) from which the drug is completely removed in a given period of time. It is expressed in ml/min or litres/hour.

$$Cl_R = \frac{\text{Rate of elimination by kidney}}{C}$$

The total body clearance, Cl_T, also called as total systemic clearance, is an additive property of individual organ clearances.

$$Cl_T = Cl_R + Cl_H + Cl_{Others}$$

$$V_d = \frac{X}{C_p}$$

C_p= Plasma drug concentration

X= Amount of drug in the body

To calculate V_d after an intravenous bolus injection eqution is rearranged.

$$V_d = \frac{X_o}{C_p{}^0}$$

X_o= is the dose of drug given by intravenous bolus.

$C_p{}^0$= extrapolated drug concentration at zero time on y-axis after drug equilibrates.

Clearance: is defined as the theoretical volume of body fluid containing drug (i.e. that fraction of apparent volume of distribution) from which the drug is completely removed in a given period of time.

For drugs given as iv bolus

$$Cl_T = \frac{X_o}{AUC}$$

One compartment open model-Intravenous infusion (Zero order absorption/ infusion rate)

Rapid iv injection is unsuitable when the drug has potential to precipitate toxicity or when maintainance of a stable concentration or amount of drug in the body is desired.

In such situation, drug (like several antibiotics, theophylline, procainamide etc.) is administered at a constant rate (zero order) by i.v. infusion.

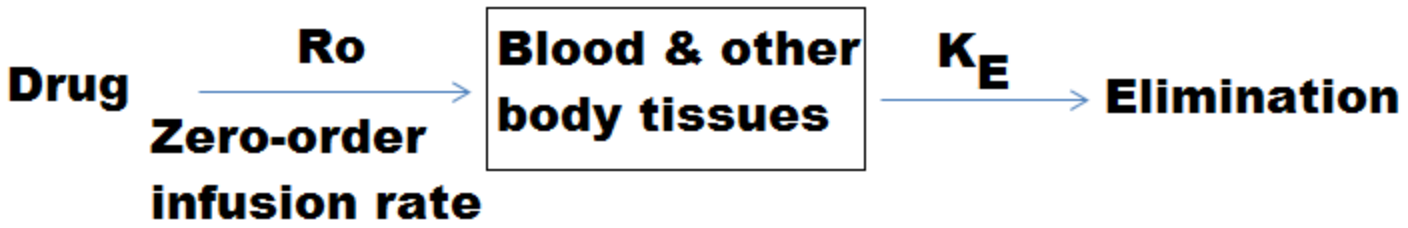
In contrast to short duration of an i.v. bolus (few seconds), the duration of constant rate infusion is usually much longer than the half-life of the drug.

Advantages of Zero order infusion of drugs

1. Ease of rate of control of infusion to fit individual patient needs.

2. Prevents fluctuating maxima and minima(peak and valleys), plasma level, desired especially when drug has narrow therapeutic index.

3. Other drugs, electrolytes and nutrients can be conveniently administered simultaneously by same infusion line in critically ill patients.



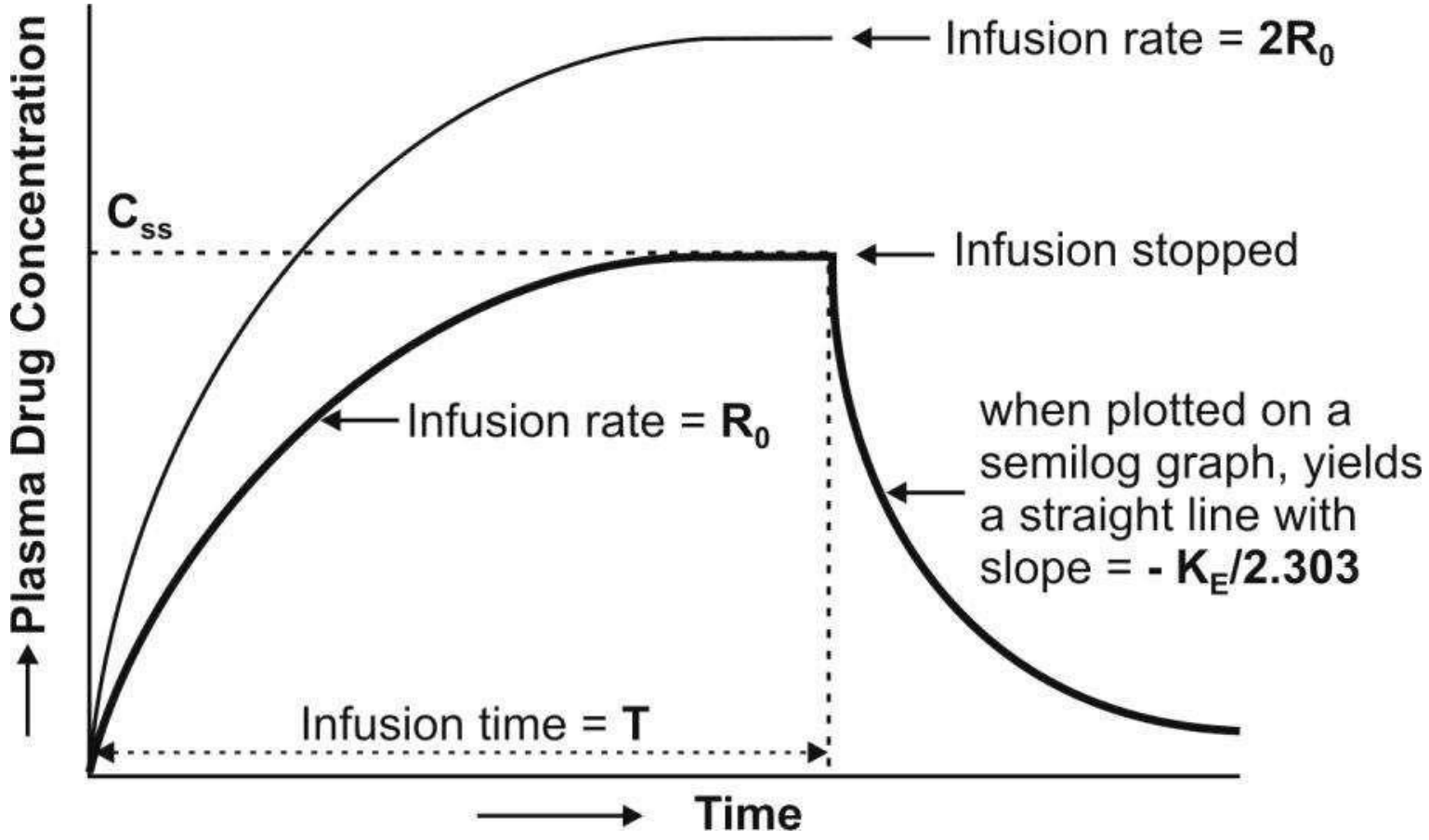
$$\frac{dx}{dt} = Rate\ in\ (availability) - Rate\ out\ (elimination)$$

$$\frac{dx}{dt} = R_0 - K_E X$$

$$\frac{dx}{dt} + K_E X = R_0$$

$$X = \frac{R_0}{K_E}$$

Plasma concentration-time profile for a drug given by constant rate i.v. infusion (the two curves indicate different infusion rates Ro and 2Ro for the same drug)



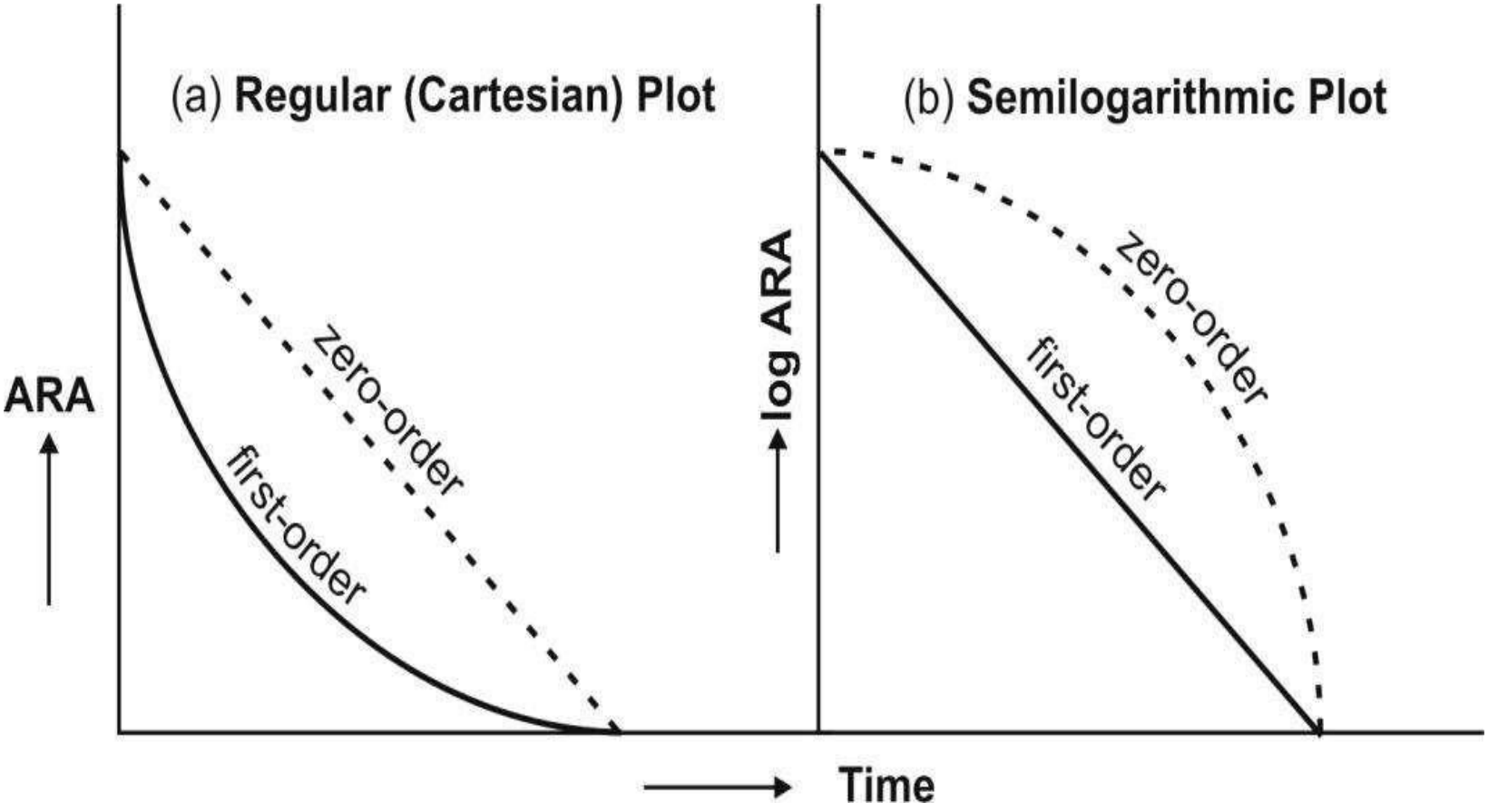
Extravascular Administration

- When a drug is administered by extravascular route (e.g. oral, i.m., rectal, etc.), absorption is a prerequisite for its therapeutic activity.

- The rate of absorption may be described mathematically as a zero-order or first-order process. A large number of plasma concentration- time profiles can be described by a one- compartment model with first-order absorption and elimination.

- However, under certain conditions, the absorption of some drugs may be better described by assuming zero-order (constant rate) kinetics.

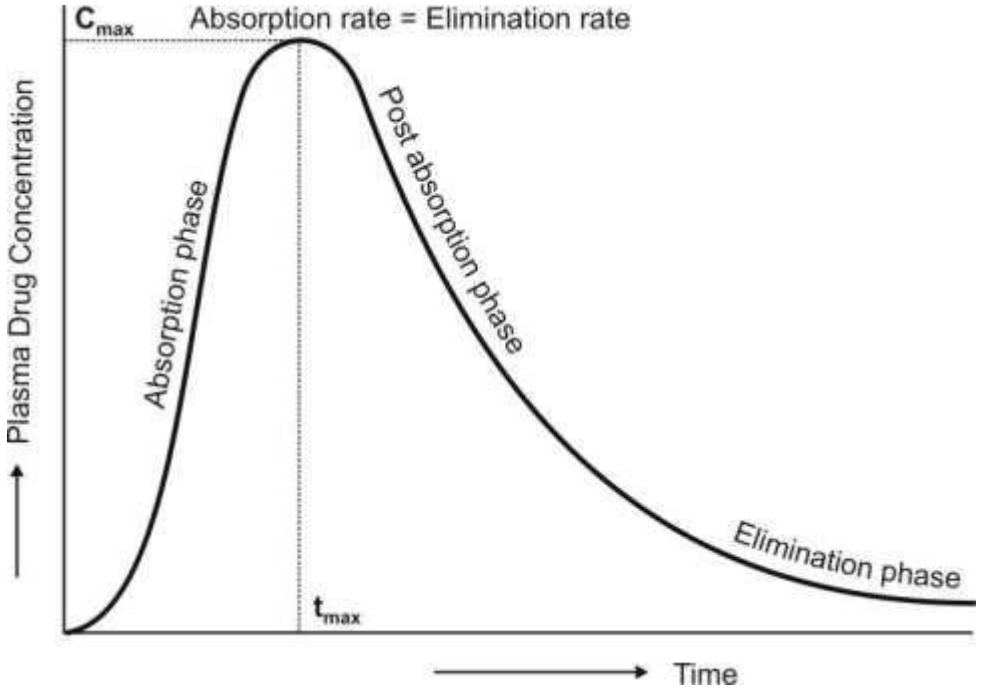
Distinction between zero-order and first-order absorption processes. Figure (a) is regular plot, and Figure (b) a semi log plot of *amount of drug remaining to be absorbed (ARA) versus time t*.



Zero-order absorption is characterized by a constant rate of absorption

dX/dt = Rate of absorption – Rate of elimination

$$\frac{dX}{dt} = \frac{dX_{ev}}{dt} - \frac{dX_E}{dt}$$




Thank
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